Neoadjuvant Docetaxel-Based Chemoradiation for Resectable Adenocarcinoma of the Pancreas

Olivier Turrini, Marc Ychou, Laurence Moureau-Zabotto, Philippe Rouanet, Marc Giovannini, Vincent Moutardier, David Azria, Jean-Robert Delpero, Frédéric Viret

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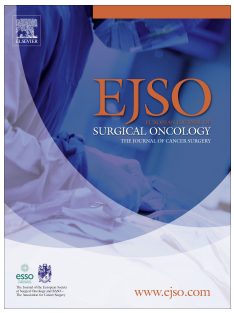

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Dear Editor,

Our manuscript '**Neoadjuvant Docetaxel-Based Chemoradiation for Resectable Adenocarcinoma of the Pancreas.'** was approved by all authors. This work was not submitted elsewhere and no authors have conflict of interests.

Olivier Turrini, MD

Department of Surgical Oncology

Purpose: to assess the safety and efficacy of a new neoadjuvant chemoradiation (CRT) docetaxel-based regimen in patients with resectable adenocarcinoma of the pancreatic head or body.

Patients and Methods: 34 patients with histologically-confirmed resectable pancreatic adenocarcinoma were included in this prospective two-center phase II study. Radiotherapy was delivered at the dose of 45 Gy in 25 fractions of 1.8 Gy per fractions, 5 days/week, over 5 weeks. Docetaxel was administered as a 1-hour intravenous (IV) infusion repeated every week during 5 weeks. The dose was 30 mg/m²/week. All patients were restaged after completion of CRT.

Results: Tumor progression was documented in 11 patients (32%), stable disease was documented in 20 patients (59%), and partial remission was documented in 3 patients (9%). 23 patients still with local disease at restaging underwent explorative laparotomy. Of this, 17 patients (50%) had a curative pancreaticoduodenectomy with lymphadenectomy. Morbidity and mortality rates were 29% and 0%, respectively. Three patients (17%) had complete histological responses and 5 patients had minimal residual disease. All resected patients (n=17) underwent R0 resection. The median and five-year survival times for the resected patients were 32 months and 41%, respectively. Among the resected patients, ten (59%) died as a result of recurrent pancreatic cancer without local tumor bed recurrence.

Conclusions: Neoadjuvant docetaxel-based chemoradiation is well tolerated. Resected patients had a prolonged survival time. Further studies are needed to confirm our findings and determine the role of such a neoadjuvant approach.

Introduction

Surgery remains the gold standard for the treatment of pancreatic carcinoma. Nevertheless, the long-term prognosis of patients with resectable cancer of the pancreatic head remains dismal, with a median overall survival of approximately 12 months after pancreaticoduodenectomy (PD) alone[1]. Tumor size, lymph node metastasis and resection margins[2] are the main factors affecting survival rate. Better patient selection and multimodality treatment concepts are crucial to improving survival. Although the addition of radiotherapy to adjuvant chemotherapy remains controversial, adjuvant chemotherapy alone has demonstrated a benefit in recurrence-free and overall survival times[3,4]. However, at least 25% of the patients at risk do not receive adjuvant treatment after PD for various reasons[5]. This major shortcoming can be prevented by the use of a neoadjuvant regimen[6,7].

Preoperative regimens for patients with resectable pancreatic cancer have only been investigated in a few studies and were based on chemoradiotherapy (CRT) in which the final resectability rates ranged between 30% and 75%[8-17] (table 1).

The aim of the current study was to assess the safety and efficiency of a new neoadjuvant CRT docetaxel-based regimen in patients with resectable pancreatic head adenocarcinoma.

Patients and Methods

Eligibility criteria

Between May 2003 and July 2005, 34 patients with histologically-confirmed pancreatic adenocarcinoma were included in this prospective phase II study. All patients were treated either at the Institut Paoli-Calmettes (Marseille, France) or at the Centre Val d'Aurelle (Montpellier, France). Patients having any major comorbidity precluding consideration of pancreatic surgery were excluded. Patients with tumor surrounding >180° of the circumference of the portal or superior mesenteric vein, or occlusion of the superior mesenteric vein (SMV) or portal vein (PV) confluence, or direct tumor extension to either the superior mesenteric artery (SMA) or the celiac axis, or with evidence of extrahepatic disease were considered non-resectable. Patients with adenocarcinoma of the tail of the pancreas, intraductal papillary-mucinous adenocarcinoma, tumors of neuroendocrine origin or patients with carcinoma of the duodenum, distal common bile duct, or Ampulla of Vater were also excluded. Patients were also required to have a Karnofsky performance status of at least 70 and a serum bilirubin level less than 10 mg/dL. Patients diagnosed with jaundice underwent primary biliary decompression. Patients with resectable disease associated with high serum CA19-9 level (>200 UI/mL) after biliary decompression were not excluded for neoadjuvant treatment or surgery as radiological staging did not detect distant metastasis. The protocol was approved by the Ethics Committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, CCPPRB) of both centers and all patients were included after informed consent.

Disease staging

Disease was affirmed and staged by physical examination, biopsy (fine needle aspiration with Wilson-Cook 22 gauge, 8 cm needles) obtained by endoscopy under ultrasound guidance (EUS) (Pentax-Hitachi, Hamburg, Germany) and thin-section contrast-enhanced helical dual phase scanning (CT scan). We used semiautomatic bolus-tracking programs provided by the manufacturers to determine the starting time for arterial phase scanning. A region of interest was drawn on the aorta at the level of the diaphragm, and the trigger level

was set at 90 HU. **Arterial phase scanning** was started 11 seconds after the aortic enhancement reached the trigger level. Scanning began at the diaphragm and continued caudally to the inferior margin of the liver during a single breath hold. Hepatic arterial phase scanning delays were 11–17 seconds after descending aorta enhancement to 100 HU, as measured with use of a bolus-tracking technique, and **portal venous phase** interscanning delays were 20–30 seconds after the aortic enhancement. Equilibrium phase images were acquired 180 seconds.

All patients were restaged after completion of CRT. Surgery was scheduled at 4–6 weeks after the end of neoadjuvant CRT. The laparoscopic approach was not routinely used.

Treatment plan

Radiotherapy was delivered at the dose of 45 Gy in 25 fractions of 1.8 Gy per fractions, five days/week, over five weeks. A CT-scan was done on all patients in order to perform a three-dimensional CT-based treatment plan. The clinical target volume (CTV) was defined by the tumor and the regional lymph nodes with a 2-cm margin. Planning target volume (PTV) was defined by CTV with a 1-cm margin. A 4-field technique was used with >6 MV photons. A cumulative dose-volume histogram was recommended: the dose to the spinal cord was limited to 35 Gy and no more than 30% of the total kidney volume received >50% of the prescribed dose.

Docetaxel was administered as a 1-hour intravenous (IV) infusion repeated every for 5 weeks. The dose was 30 mg/m²/week. A preliminary Phase I study had established the exact amount of docetaxel to be administered in combination with radiotherapy localized to the pancreas[18]. All patients received dexamethasone 8 mg orally at 12, 7 and 1 hour(s) before docetaxel and again at 12 hours following docetaxel administration. Complete blood cell counts were measured weekly. If the leukocyte count was $\geq$ 2 x 10^9/l and platelets $\geq$ 100 x 10^9/l, a full dose of docetaxel was administered.

Week 1 Week 2 Week 3 Week 4 Week 5

EBRT, 45 Gy, 25 fractions

D **D** **D** **D** **D**

(**D**: **D**OCETAXEL 30 mg/m²/week; **EBRT**: **E**xternal-**B**eam **R**adiation **T**herapy)

World Health Organization (WHO) Grade 2, 3 or 4 toxicity events were recorded during CRT.

Surgery

Surgery was performed through a bisubcostal incision. Exploration was done to identify the presence of liver metastases or carcinomatosis. Assessment of local invasion was begun by dissection of the SMA and eventual biopsy of vessel walls. Patients with tumor located in the pancreatic body (n=15) underwent PD; no patients had mid-gland resection to avoid positive right pancreatic margins and ensure optimal clearance of retropancreatic soft tissues. PD was associated with superior mesenteric artery lymphadenectomy to obtain optimal retropancreatic clearance. Extended lymphadenectomy included dissection of the PV, peripancreatic and paraduodenal nodes, dissection of the uncinate process, and complete removal of the aortocaval nodes behind the pancreas. The lymph node dissection included the celiac axis nodes, those along the hepatic artery with dissection of the root of the right gastric artery, and a SMA lymphadenectomy. A Child procedure was routinely performed.

Radiological Tumor Response

Radiological tumor response was determined using Response Evaluation Criteria in Solid Tumors (RECIST) criteria for staging and restaging on CT scans.

Histological analysis

Specimens were routinely stained to assess various resection margins: portal vein bed, pancreatic section and retroportal bed. Margin positivity was defined by the presence of tumor at or <=1 mm of a margin when assessed by microscopy. Tumor size, number and status of lymph nodes, and resection margins were noted. Staging was done according to the TNM classification of the American Joint Committee on Cancer. The absence of residual cancer in the resected specimen after RCT was defined as a complete pathologic response (Stage 0) and a partial histological response with minimal residual disease (> 50% tumor

destruction). The tumor was Stage I or IIA (ypT1 or ypT2, N0, M0) if it was localized and involved only the pancreas, bile duct and/or duodenum. If the tumor invaded regional lymph nodes, it was Stage IIB (ypT1-3, N1, M0). A tumor was Stage III if neoplastic disease was growing outside the pancreas into nearby large blood vessels or major nerves with or without involving lymph nodes (ypT4, N0-1, M0). Metastases extending beyond regional lymph nodes defined Stage IV disease (any T, any N, and M1).

Study Endpoints, ***Data Collection and Statistical Analysis***

The study end point was the resectability rate ($\geq$60%) based on the restaging procedures. If a tumor was found to be unresectable only on surgical exploration, nonresectability was not attributed to neoadjuvant chemoradiation because resectability was presumably also misdiagnosed by the initial staging. On the basis of this assumption a total of 34 patients were required according to Simon's two-stage phase II design to achieve a power of 80% ($p<0.05$). The risk of rejecting an effective treatment or of accepting an ineffective treatment is 10% each.

Mortality was calculated for the post-operative period covering 30 days after surgery or until hospital discharge. All living patients were evaluated by combined medical and surgical teams at one, four and six months postoperatively and every six months thereafter. Staging always involved physical examination, thin-section contrast- enhanced helical dual phase CT scan and tumor markers (CEA, CA 19-9). The type of recurrence was also noted (metastasis/carcinomatosis, local recurrence).

Survival was measured from the date of diagnosis to the date of death or January 1, 2009, the censor date. Survival was examined using the Kaplan-Meier method. Statistical comparisons were conducted using the log rank and Wilcoxon methods.

Results

The median time between diagnosis and the beginning of chemoradiation was 35 days (range 15- 68). The median time between diagnosis and surgery was 3.5 months (range 2.9-8.7). Patient characteristics are summarized in table 2.

Treatment outcome and resectability

Neoadjuvant CRT was delivered on an outpatient basis in all 34 patients. Thirty-one patients (91%) received the complete CRT regimen. A total 23 of 34 patients (68%) were found to have resectable disease upon restaging. Thus, 11 patients had disease progression and did not undergo surgery: 9 patients developed distant metastasis and 2 patients had local progression of the tumor with vascular involvement precluding surgery. During explorative laparotomy (n=23), 17 were found to have resectable disease and underwent PD (50%). Reasons for non-resection were carcinomatosis in three patients, liver metastases in two patients, and involvement of the SMA in one patient. PV resection was needed in five patients due to macroscopic suspicion of invasion, microscopically confirmed in one patient. Morbidity and mortality rates were 29% and 0%, respectively. One patient experienced a pancreatic fistula grade A. No patients developed postoperative hemorrhage.

Toxicity

Adverse effects during CRT are summarized in table 3. No patients experienced grade 4 toxicity.

Radiological tumor response

Twenty-seven patients were submitted to echo-endoscopy to determine the post-CRT/pre-surgery diameter of the tumor. The diameter remained unchanged before (median: 3 cm, range 2-6.5) and after (median: 3 cm, range 0-6.5) CRT. According to the RECIST evaluation of tumor response, tumor progression was documented in 11 patients (32%), stable disease was documented in 20 patients (59%), and partial remission was documented in three patients (9%).

Pathological findings

Three patients (17%) had complete histological responses (stage 0) and five patients had minimal residual disease. Tumor fibrosis was present in all specimens. Regional lymph nodes were involved in four patients (24%). All resected patients (n=17) underwent R0 resection.

Disease Recurrence

Among the resected patients, ten (59%) died as a result of recurrent pancreatic cancer without local tumor bed recurrence. The liver was the most common site of tumor recurrence (7 of 10 patients, or 70%). Carcinomatosis occurred in two patients (20%) and lung metastasis in one patient (10%).

Survival (figure 1)

No patients were lost to follow-up through the censor date of January 1, 2009. Median time of follow-up was 54 months (range 38-65). The median overall survival for all patients (n=34) was 15.5 months (95% CI [12.1-31.9]); the five-year survival for all 34 patients was 20.6% (95% CI [10.6-39.8]).

Median survival for resected (n=17) vs. unresected (n=17) patients was 32 months (95% CI [22.3-37.2]) and 11 months (95% CI [7.3-14.7]), respectively (p<0.001). The five-year survival for resected vs. unresected patients was 41% and 0% (p<0.001), respectively. The overall progression-free survival for resected patients was 23 months (95% CI [21.5-24.5]).

Discussion

Cancer of the pancreatic head is considered locally resectable when infiltration of surrounding organs and arteries is absent. After curative resection, adjuvant chemotherapy improves survival[3,4] but at least 25% of patients cannot receive this treatment because of complications related to surgery[5].Thus, several teams have supported the use of preoperative (neoadjuvant) treatment[8-17] offering several theoretical advantages such as a multimodal treatment concept for all patients, a potentially higher R0 resection rate, and the treatment of micrometastases before surgery when using neoadjuvant chemotherapy. Moreover, in our study, we noticed that 14 patients (41%) developed distant metastases during CRT, at restaging or during explorative laparotomy. Thus, resection could be avoided and, as published by several teams[16], neoadjuvant treatment should combine chemotherapy followed by CRT in patients without distant metastasis detected at restaging after completion of chemotherapy. On the other hand, this concept harbors the risk of disease progression during therapy because of the aggressiveness of the tumor or due to ineffective treatment. Indeed, 3 patients (9%) who had resectable disease at diagnosis had local tumor progression during CRT and subsequently did not have curative PD.

After having initially tested the docetaxel/radiotherapy combination in a phase I study[18], we are now presenting our results for the neoadjuvant approach. A total 91% of patients were able to receive complete pre-operative treatment, even with the elevated intensity dose of docetaxel (30 mg/m²/week, a dose within the range of the DMT gained from docetaxel used alone). Gemcitabine studies have also reported good feasibility (>80% of patients receive the entire treatment) but with a reduced intensity dose[19]. Our strategy of a minimal radiotherapy (45 GY over a 5-week period instead of 50.4 GY) was based on the presumed toxicity of our chemotherapy regimen. However, we remarked the feasibility of a low toxicity docetaxel/radiotherapy treatment when used in a neoadjuvant setting for the treatment of locally resectable pancreatic adenocarcinoma.

The resectability rate on restaging examinations was 68% and the definitive resectability rate

after explorative laparotomy was 50%. This rate was lower than the resectability rate already published in patients receiving neoadjuvant chemoradiation (table 1). We did not use high CA19-9 serum levels to exclude patients for surgery. However, it is now accepted that a CA19-9 rate above 200-400 U/ml is a poor prognostic factor even for patients presenting with resectable pancreatic carcinoma without distant metastasis detected at preoperative staging[20]. Moreover, Maithel et al. recently reported a benefit matching CA19-9 serum level (over 130 U/mL) and a laparoscopic approach to avoid unnecessary laparotomy[21]. In hindsight, using both CA19-9 serum levels and laparoscopic staging might have decreased our disease progression rate during neoadjuvant treatment and improved our resection rate, thus optimizing patient selection for our study. Furthermore, we now speculate that patients with high serum CA19-9 levels may benefit from a neoadjuvant sequence of chemotherapy (gemcitabine) followed by CRT. After completion of chemotherapy, and prior to CRT, patients could be restaged and those with metastases could avoid subsequent radiation and surgical insults[16]. Our study included patients with adenocarcinoma of the pancreatic body (n=15) that likely involved nearby vascular structures (SMA, celiac axis, PV). Thus, these patients have a reduced probability of resection and we supposed that including only patients with cephalic head adenocarcinoma would increase our resectability rate.

Surgery without preoperative treatment leads to more than 70% positive resection margins[22]. The local control provided by neoadjuvant CRT is difficult to ignore: findings of complete pathologic response, a low incidence of metastatic lymph nodes, a low incidence of margin positivity and absence of local recurrences when compared with patients who did not undergo neoadjuvant treatment[9,23-26] are compelling arguments for the local impact of chemoradiation[8-10,13,14,17,27-29,] These findings are consistent with those noted in other series using neoadjuvant CRT.

Despite the fact that the small number of patients included in our series precludes emphatic conclusions, we noticed an improved survival rate in patients undergoing the planned treatment (neoadjuvant CRT and PD). Indeed, the median survival time was 31.9 months and five-year survival estimate was 41%. Recent series reporting the use of neoadjuvant

chemotherapy followed by chemoradiation showed similar survival rates[16]. However, we believe that further studies on docetaxel-combined chemoradiation are needed to confirm our findings. Moreover, toxicity was acceptable and we hypothesize that neoadjuvant chemotherapy followed by docetaxel-based CRT should improve our actual results.

Conclusions

Neoadjuvant docetaxel-based chemoradiation for resectable pancreatic adenocarcinoma was safe, well-tolerated and showed improved survival rates. Screening patients with high serum CA19-9 levels with staging laparoscopy and employing “screening” systemic chemotherapy prior to neoadjuvant CRT might improve patient survival and selection of patients who may most benefit from such an approach. Pancreatic cancer treatment clearly needs more effective therapies, but also needs to balance treatment decisions with proper attention to patients’ quality of life. Patients with micrometastases who will likely not benefit from local control treatments such as surgery or radiation should be optimally excluded from surgical and radiation-based treatment approaches.

References

1. Traverso LW. Pancreatic cancer: surgery alone is not sufficient. Surg Endosc. 2006 Apr;20 Suppl 2:S446-9.
2. Cleary SP, Gryfe R, Guindi M et al. Prognostic factors in resected pancreatic adenocarcinoma: analysis of actual 5-year survivors. J Am Coll Surg. 2004 May;198(5):722-31.
3. Neoptolemos JP, Stoken DD, Friess H et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med, 2004. 350(12): 1200-10.
4. Oettle H, Post S, Neuhaus P et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. Jama, 2007. 297(3): p. 267-77.
5. Aloia TA, Lee JE, Vauthey JN et al. Delayed recovery after pancreaticoduodenectomy: a major factor impairing the delivery of adjuvant therapy? J Am Coll Surg. 2007 Mar;204(3):347-55.
6. Crane CH, Varadhachary G, Wolff RA et al., The argument for pre-operative chemoradiation for localized, radiographically resectable pancreatic cancer. Best Pract Res Clin Gastroenterol, 2006. 20(2): p. 365-82.
7. Wayne JD, Abdalla EK, Wolff RA et al. Localized adenocarcinoma of the pancreas: the rationale for preoperative chemoradiation. Wayne JD, Abdalla EK, Wolff RA, Crane CH, Pisters PW, Evans DB. Oncologist. 2002;7(1):34-45.
8. Evans DB, Rich TA, Byrd DR et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas.Arch Surg. 1992 Nov;127(11):1335-9.
9. Spitz FR, Abbruzzese JL, Lee JE et al. Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas.J Clin Oncol. 1997 Mar;15(3):928-37.
10. Hoffman JP, Lipsitz S, Pisansky T et al. Phase II trial of preoperative radiation therapy and chemotherapy for patients with localized, resectable adenocarcinoma of the pancreas: an Eastern Cooperative Oncology Group Study.J Clin Oncol. 1998 Jan;16(1):317-23.
11. Snady H, Bruckner H, Cooperman A et al. Survival advantage of combined chemoradiotherapy compared with resection as the initial treatment of patients with regional pancreatic carcinoma. An outcomes trial. Cancer. 2000 Jul 15;89(2):314-27.
12. Breslin TM, Hess KR, Harbison DB et al. Neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreas: treatment variables and survival duration. Ann Surg Oncol. 2001 Mar;8(2):123-32.
13. White RR, Hurwitz HI, Morse MA et al. Neoadjuvant chemoradiation for localized adenocarcinoma of the pancreas.Ann Surg Oncol. 2001 Dec;8(10):758-65.

14. Mehta VK, Fisher G, Ford JA et al.Preoperative chemoradiation for marginally resectable adenocarcinoma of the pancreas.J Gastrointest Surg. 2001 Jan-Feb;5(1):27-35.
15. Evans DB, Varadhachary GR, Crane CH et al. Preoperative Gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. J Clin Oncol 2008 20;26(21):3496-502.
16. Varadhachary GR, Wolff RA, Crane CH et al. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. J Clin Oncol. 2008 Jul 20;26(21):3487-95.
17. Turrini O, Viret F, Moureau-Zabotto L et al. Neoadjuvant 5 fluorouracil-cisplatin chemoradiation effect on survival in patients with resectable pancreatic head adenocarcinoma: a ten year single institution experience. Oncology. 2009;76(6):413-9.
18. Viret F, Ychou M, Gonçalves A et al. Docetaxel and radiotherapy and pancreatic cancer. Pancreas. 2003 Oct;27(3):214-9.
19. Talamonti MS, Small W Jr, Mulcahy MF et al., A multi-institutional phase II trial of preoperative full-dose gemcitabine and concurrent radiation for patients with potentially resectable pancreatic carcinoma. Ann Surg Oncol, 2006. 13(2): p. 150-8.
20. Ferrone CR, Finkelstein DM, Thayer SP et al. Perioperative CA19-9 levels can predict stage and survival in patients with resectable pancreatic adenocarcinoma. J Clin Oncol. 2006 Jun 20;24(18):2897-902.
21. Maithel SK, Maloney S, Winston C et al. Preoperative CA 19-9 and the yield of staging laparoscopy in patients with radiographically resectable pancreatic adenocarcinoma. Ann Surg Oncol. 2008 Dec;15(12):3512-20.
22. Esposito I, Kleeff J, Bergmann F et al. Most pancreatic cancer resections are R1 resections. Ann Surg Oncol. 2008 Jun; 15(6).
23. Griffin JF, Smalley SR, Jewell W et al. Patterns of failure after curative resection of pancreatic carcinoma. Cancer 1990; 66:56-61.
24. Kayahara M, Nagakawa T, Ueno K et al. An evaluation of radical resection for pancreatic cancer based on the mode of recurrence as determined by autopsy and diagnostic imaging. Cancer 1993; 72:2118-23.
25. Nitecki SS, Sarr MG, Colby TV et al. Long-term survival after resection for ductal adenocarcinoma of the pancreas. Is it really improving? Ann Surg 1995; 221:59-66.
26. Sperti C, Pasquali C, Piccoli A et al. Recurrence after resection for ductal adenocarcinoma of the pancreas. World J Surg. 1997 Feb;21(2):195-200.).
27. Turrini O, Viret F, Moureau-Zabotto L et al. A modified Dworak classification applied to pancreatic adenocarcinoma: a useful prognostic factor. Bull Cancer. 2007 Oct 1;94(10)
28. Sasson AR, Wetherington RW, Hoffman JP et al. Neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreas: analysis of histopathology and outcome. Int J Gastrointest Cancer 2003; 34:121-8
29. White RR, Xie HB, Gottfried MR et al. Significance of histological response to preoperative chemoradiotherapy for pancreatic cancer. Ann Surg Oncol 2005; 12:212-21

Table 1: Resection rate and survival of series with 5-Fu based neoadjuvant CRT.

	year	n	Resection rate	Median survival, all patients (months)	Median survival, resected patients (months)
Evans et al.[8]	1992	28	17/28 (61%)	-	-
Spitz et al.[9]	1997	91	41/91(45%)	-	19.2
Hoffman et al.[10]	1998	53	24/53 (45%)	9.7	15.7
Snady et al.[11]	2000	68	20/68 (30%)	23.6	32.3
Breslin et al.[12]	2001	132	-	-	21
White et al.[13]	2001	68	20/68 (30%)	-	Non reached at 16 months
Mehta et al.[14]	2001	15	9/15 (60%)	-	30
*Evans et al.[15]	2008	86	64/86 (74%)	22.7	34
*Varadhachary et al.[16]	2008	90	52/79 (66%)	17.4	31
Turrini et al.[17]	2008	102	62/101 (61%)	17	23
Current series	2009	34	17/34 (50%)	15.5	31.9

*gemcitabine-based neoadjuvant CRT or preoperative chemotherapy followed by gemcitabine-based CRT

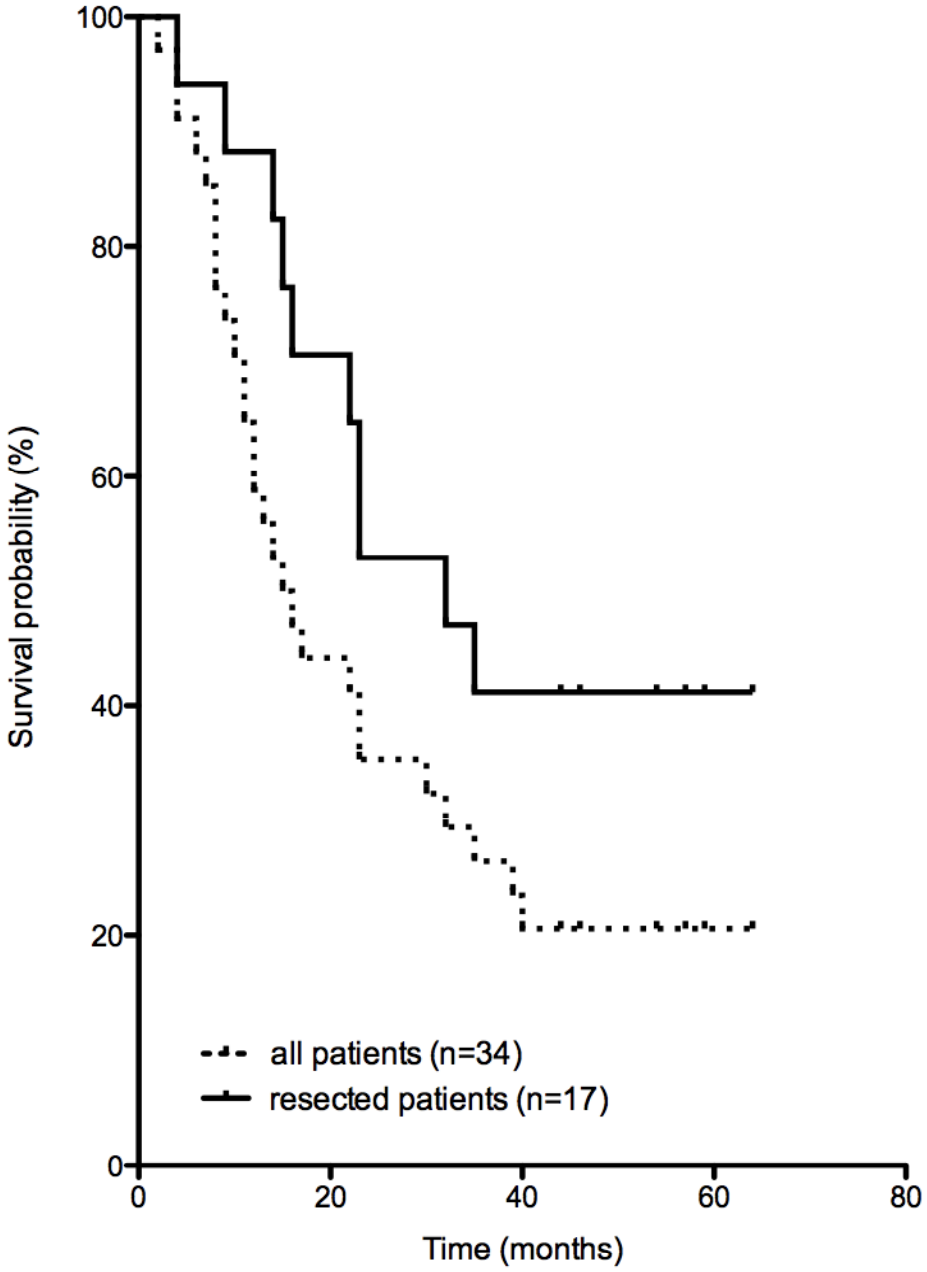
Table 2: Baseline Patient Characteristics

Characteristics	
Mean age	61.5 range [40-72]
Gender	
Male	21
Female	13
Tumor localization	
Head	18
Body	15
Median tumor size (cm)	2.95 range [1.4-6.5]
Pretreatment US staging	
T1	7
T2	25
T3	2
Median pretreatment CA19.9 (UI/ml)	114 range [1-9432]
ECOG status	
0	21
1	12
2	1

Table 3: toxic events during RCT according to WHO classification.

	grade 2	grade 3	grade 4	grade 5	Total
Digestive	10	2	-	-	12 (35%)
Biliary sepsis	*2*	-	-	-	
Nausea / vomiting	*4*	*2*	-	-	
Diarrhea	*4*	-	-	-	
Weight loss	11	-	-	-	11 (32%)
Fever	5	-	-	-	5 (15%)
Hematologic	6	-	-	-	6 (18%)
Skin	1	-	-	-	1 (3%)
Patients	**11 (32%)**	**2 (6%)**	**0**	**0**	**13 (38%)**

Figure 1: Overall Survival on intention-to-treat analysis (n=34) and of patients after pancraticoduodenectomy (n=17) patients



Subjects at risk

Months	**0**	**12**	**24**	**36**	**48**	**60**
All	34	22	14	10	5	2
Resected	17	16	11	8	5	2